

# COMPARISON OF ORAL 25-HYDROXYCHOLECALCIFEROL, VITAMIN D, AND ULTRAVIOLET LIGHT AS DETERMINANTS OF CIRCULATING 25-HYDROXYVITAMIN D

T. C. B. STAMP J. G. HADDAD  
C. A. TWIGG

Royal National Orthopaedic Hospital and Middlesex Hospital,  
London, and Jewish Hospital of St. Louis, U.S.A.

**Summary** Circulating concentrations of 25-hydroxyvitamin D (25-OHD) were measured during short-term and long-term oral treatment with 25-hydroxycholecalciferol (25-OHD<sub>3</sub>, 25-H.C.C.) or with vitamin D in over 200 subjects over a period of 5 years. Ten times more vitamin D than 25-OHD<sub>3</sub> was required to produce equivalent plasma-25-OHD concentrations. Plasma-25-OHD was a power function of dosage with both compounds. These data indirectly measure the superior therapeutic potency of 25-OHD<sub>3</sub> show that dose-response relations with both compounds may be useful in diagnosis, and indicate that there are pronounced constraints on 25-hydroxylation of vitamin D. Together with the effects of ultraviolet light, now shown to be equivalent to oral vitamin D in doses of 8000-10 000 I.U. daily, these constraints may protect against vitamin-D deficiency in winter.

## Introduction

PLASMA-25-HYDROXYVITAMIN-D (25-OHD) is often measured as an index of response to various forms of vitamin-D treatment. Although preliminary data have been obtained during pharmacological oral dosage,<sup>1</sup> analysis of plasma-25-OHD as a function of dosage is lacking. 25-hydroxycholecalciferol (25-OHD<sub>3</sub>, 25-H.C.C.) is several times more potent than the parent vitamin, but reports of its therapeutic efficacy have not included systematic measurement of plasma concentrations.<sup>2,3</sup> Vitamin D is a pro-hormone<sup>4</sup> which only becomes active on transformation to its 25-hydroxy derivative, a process that is subject to pronounced but poorly understood constraints.<sup>5-7</sup>

Comprehensive comparison of plasma-25-OHD concentrations during treatment with the two compounds should both clarify the extent of these constraints in man and indirectly measure the relative therapeutic potencies of the two compounds. As a further result, previous data on natural<sup>8</sup> and artificial<sup>9,10</sup> ultraviolet light could be more critically evaluated.

## DR RILEY AND OTHERS: REFERENCES

1. Riley, I. *Papua N.G. med. j.* 1973, **16**, 9.
2. *Lancet*, 1969, **ii**, 1187.
3. Devitt, I., Douglas, R. *Med. J. Aust.* 1973, **i**, 49.
4. Harman, D., Glasgow, H., Sturt, J., Devitt, I., Douglas, R. *New Engl. J. Med.* 1971, **284**, 175.
5. Harman, D., Devitt, I., Miles, H., Riley, I. *Med. J. Aust.* 1974, **ii**, 353.
6. Woodcock, A., Blackburn, C. *Australas. Ann. Med.* 1967, **1**, 11.
7. Schiffman, C., Austrian, R. *Fedin. Proc.* 1971, **30**, 658.
8. MacLeod, C., Hodges, R., Heideberger, M., Bernhard, W. *J. Exp. Med.* 1945, **82**, 445.
9. Austrian, R., Douglas, R., Schiffman, G., Coetzee, A., Koorhof, H., Hayden Smith, S., Reid, R. *Trans. Am. Phys. Soc.* 1976, **89**, 184.
10. Heideberger, M., deLapi, M., Walker, A. *J. Immun.* 1950, **65**, 535.

involved vaccine and 6012 received a saline placebo. In the first 3 years after vaccination 303 people died—170 placebo and 133 vaccine. This represents a 22% difference in mortality and a crude difference of almost 2 deaths per 1000 persons. The difference was largely due to fewer deaths from respiratory causes (table iv). The most significant difference was in deaths from pneumonia uncomplicated by chronic lung disease—41 placebo and 23 vaccine. This represents a 42% difference in mortality which is significant at the  $p < 0.05$  level. There was far less protection given to persons suffering from chronic lung disease (table v).

During an epidemic of influenza in early 1976 there were 25 deaths due to respiratory causes—16 placebo and 9 vaccine. The difference is not significant but does suggest a protection rate of 40% which is consistent with other results.

## Discussion

The vaccine reduced the alveolar multiplication of pneumococci and their invasion of the bloodstream, but had little effect on their invasion of the lower respiratory tract. The severity rather than the incidence of pneumonia was affected, and mortality-rates were reduced accordingly.

These results differ in some ways from those reported by MacLeod et al. in 1945,<sup>8</sup> and more recently by Austrian et al.<sup>9</sup> Both these trials of pneumococcal polysaccharide vaccine dealt with large populations of young men: U.S. Army recruits and South African mine workers respectively. The incidence of pneumonia was high, and this could largely be attributed to the exposure of healthy recruits to respiratory pathogens with which they had no previous contact. Immunisation not only reduced the incidence of pneumonia and of blood-borne pneumococcal invasion, but also reduced sputum and nasopharyngeal isolation rates of the organisms.

The susceptibility of the Huli people to pneumonia has several causes. They live in poorly ventilated, smoky huts and are often exposed to a cold wet climate; chronic lung disease with associated damage to respiratory defences and bacterial contamination of the respiratory tract is common. This, together with the comparatively high pre-immunisation levels of antibody, may explain why the vaccine had no effect on sputum and nasopharyngeal isolation of the pneumococcus.

Two important facts emerge from this study: the vaccine has reduced mortality from pneumonia, and the reduction occurred steadily over 3 years. The steady decline is consistent with earlier findings that the level of antibodies to pneumococcal polysaccharide remains at half its maximum value 5 years after immunisation.<sup>10</sup> The reduction in mortality is clearly important to health care in the underdeveloped world. The vaccine is a useful adjunct to primary health-care services. It may alleviate the crippling effects of influenza on Highlands communities.

The trial was supported by the Department of Public Health, Papua New Guinea, and by a grant from Merck, Sharp and Dohme Limited, who also provided the vaccine. Serum-antibody estimations were performed by Dr M. D. Bonner in the laboratories of Prof. R. Austrian. Field work was carried out by B. Iwas, K. Kipusu, J. Borwick, P. Agius, D. Kane, D. Holliday, and many others. We gratefully acknowledge the encouragement of Dr R. F. R. Scragg and of Professor Austrian.

Requests for reprints should be addressed to I.D.R., 2 Albany Crescent, East Killara, N.S.W. 2071, Australia.

References at foot of next column



achieved by a dose of vitamin D that was at least ten times greater. Plateau concentrations were achieved in six weeks with 25-OHD<sub>3</sub>, whereas with vitamin-D treatment this could take four months, and similar periods of time were required for concentrations to return to the physiological range on stopping treatment (unpublished).

Changes in plasma-25-OHD during long-term solar irradiation<sup>10</sup> or short-term ultraviolet therapy<sup>11,12</sup> have been previously reported. The present comparison now shows that these changes are equivalent to those produced by a daily dose of 10 000 I.U. oral vitamin D in—i.e., 100 times the recommended daily adult dietary intake.<sup>16</sup> While there are several reservations against accepting this figure as representing endogenous synthesis, including the relative availability to liver of endogenous and exogenous vitamin D, our data raise a further aspect of vitamin-D economy, namely that synthesis of considerable amounts of the pro-hormone<sup>1</sup> in summer coupled with the pronounced constraints on its subsequent 25-hydroxylation may provide some protection against deficiency in winter.

## Reviews of Books

### The Treatment of Venous Disorders

Edited by JOHN T. HOBBS, St Mary's Hospital, London. Lancaster: M. P. P. 1977. Pp. 438. £12.50.

COMING during a spate of publications on the pathology and surgery of the venous system, this book might easily have been repetitive. That it is not is a credit to its editor. By collecting an international panel of experts he has filled in many gaps not covered in British textbooks and has expanded many aspects of the subject which have already been dealt with. The title is misleading, for a good deal more than treatment is dealt with. There are contributions on aetiology, prevention, and radiological investigation, isotope screening, and venous-pressure measurements in the investigation of peripheral venous disorders. The seven contributions on the treatment of varicose veins are especially good: seven authors from seven countries are widely, if predictably, in their use of surgery and injection sclerotherapy. K. Sigg from Switzerland is the chief advocate for sclerotherapy, while R. A. Nabatoff from the U.S.A. condemns all but operative surgery. F. Bezzoni of Russia has an approach similar to that of most clinicians in Britain—injection sclerotherapy for small, below-knee varices and high ligation and stripping for gross main-stem incompetence. Mr Hobbs' own controlled trial with similar conclusions constitute the bulk of his contribution on the subject. It is a pity that the prevention and treatment of deep-vein thrombosis could not similarly have been dealt with by a series of authors, but the subject is now so large and opinion so divided that the most unduly volume would doubtless have resulted. A. N. Nicolaides, I. Gordon-Smith, and J. D. Lewis deal clearly with these subjects. Although low-dose subcutaneous heparin is preferred in prophylaxis, other methods are fully described and given fair coverage, but not everyone will agree that compression bags and dextran give rise to logistic problems or circulatory overloading. Vascular surgery will be mostly interested in the second half of the book. Here the difficult subjects of major vein replacement in venous trauma and in the postphlebotic syndrome are dealt with by J. Volfart of Germany, A. V. Mikrovsky and L. I. Kloner of Russia, E. A. Hushi from Ohio, and R. W. Hobson, H. M. Rich, and C. B. Wright from Washington, U.S.A. These subjects have not previously been dealt with in depth in any English language textbook and certainly not by a similarly distinguished international panel of experts.

We thank Dr H. N. Fearnley for statistical help and the Wellcome Trust and the National Institutes of Health (grant AM-14570) for financial support.

Requests for reprints should be addressed to T. C. B. S., Royal National Orthopaedic Hospital, 234 Great Portland Street, London W1N 6AD.

## REFERENCES

1. Haddad, J. G., Stamp, T. C. B. *Am. J. Med.* 1974, **57**, 57.
2. Balaban, S., Garabedian, M. *J. clin. Invest.* 1972, **51**, 749.
3. Stamp, T. C. B., Round, J. M., Rowe, D. D. F., Haddad, J. G., *Br. med. J.* 1972, **ii**, 9.
4. Rutherford, W. E., Blondin, J., Hruska, K., Kopelman, R., Klahr, S., Slatorpolsky, E. *Kidney Int.* 1975, **8**, 320.
5. Fietelbaum, S. L., Bone, J. M., Seem, P. M., Galdes, J. J., Bates, M., Bousquet, V., Avioli, L. V. *J. Am. med. Ass.* 1976, **235**, 164.
6. Ondaal, J. L., Deluca, H. F. *Physiol. Rev.* 1973, **53**, 167.
7. Bhattacharya, M. H., Deluca, H. F. *J. Biol. Chem.* 1973, **248**, 2969.
8. Bhattacharya, M. H., Deluca, H. F. *End. J.* 1973, **248**, 2974.
9. Deluca, H. F. *Am. J. Med.* 1974, **57**, 1.
10. Haddad, J. G., Chyu, K. J. *J. clin. Endocrinol. Metab.* 1971, **33**, 992.
11. Dem, C. E., Round, J. M., Rowe, D. J. F., Stamp, T. C. B. *Lancet*, 1973, **ii**, 1282.
12. Stamp, T. C. B. *Proc. Nutr. Soc.* 1975, **34**, 119.
13. Mawer, E. B., Backhouse, J., Holman, C. A., Lumb, G. A., Stanbury, S. W. *Clin. Sci.* 1972, **43**, 413.
14. Lumb, G. A., Mawer, E. B., Stanbury, S. W. *Am. J. Med.* 1971, **50**, 421.
15. Stamp, T. C. B. *Lancet*, 1974, **ii**, 121.
16. F. A. O. Nutrition Meetings Report Series no. 41. *Tech. Rep. Ser. Wild Health Org.* 1970, **452**, 34.

The result is most stimulating for those with a special interest in these difficult problems. Parsons of St. Mary's Hospital contributes an elegant chapter on the history of venous transplantation. The book is well produced and well illustrated, and its editor and publishers are to be congratulated.

### Quality Control in Clinical Chemistry

T. P. WHITEHEAD, PH.D. department of clinical chemistry, Queen Elizabeth Medical Centre, Birmingham. London and New York: Wiley, 1977. Pp. 130. £11.518.50.

THIS is a personal account of some important aspects of quality control, based on experience gained from the work of hospital routine clinical-chemistry laboratories, but with the message clearly intended also to influence the practice of clinical research laboratories. The book is easy to read, but in parts it is surprisingly insubstantial, especially considering its price. To profit from it, readers must be prepared to accept Professor Whitehead's dogmatic, colloquial, and sometimes repetitious style; they must also be on the look out for the many proof-reading errors, mostly minor but occasionally liable to mislead. Readers must also accept the author's decision to attach a new meaning to the term "variance", different from the meaning that is well established in statistical usage; variability or unreliability would have served his purpose equally explained. Fundamental concepts that could have been better explained include accuracy and imprecision, and the difference (if there is one) between true results and correct values is not made clear. In this area terminology is important; for clarity of communication, the author should have adhered closely to internationally recommended definitions. The subdivision of techniques of quality control into five stages, each clearly explained, is the most valuable contribution of this book to future improvements in the reliability of clinical chemistry—indeed, the first four stages can be applied to other laboratory disciplines. The other feature to commend especially is the comprehensive account of the U. K. National Quality Control Scheme, as an example of the fifth stage of quality control. The U. K. scheme is a system of interlaboratory (external) quality control that is associated with Professor Whitehead, and one in which clinical chemistry has given an important lead to other laboratory disciplines. The chapters on the national scheme bring together, and add to, accounts that have been published in journals. These are the aspects for which the book can be particularly commended, since the subjects described fill important gaps in the already voluminous literature on quality control.